REMARKS

Pursuant to the entry of the instant amendment, claims 1-6 and 8-14 are presently pending. At the outset, Applicants wish to thank Examiners Deberry and Allen for taking the time to meet with Applicants' representative to discuss the proposed response. Applicants submit that the instant remarks not only address the grounds of rejection set forth in the outstanding Non-Final Rejection of January 22, 2008 but also the concerns raised by the Examiners in the course of the interview of April 10, 2008 and suggestions set forth therein. In particular, to expedite prosecution and further distinguish the claimed invention from the cited prior art, Applicants have herewith amended independent claim 1 to include the limitations of now cancelled claim 7, namely to specify that the pH of the claimed formulation ranges from 5.9 to 6.8. Applicants reiterate that such amendment is presented solely for the purpose of expediting prosecution and should not be construed as Applicants agreement with or acquiescence to the grounds of rejection previously set forth.

Pursuant to Non-Final Office Action of January 22, 2008, all claims stand rejected as anticipated and/or obvious in view of the cited prior art. Applicants respectfully disagree and request reconsideration and withdrawal of the outstanding rejections in view of the following remarks:

Rejections under 35 U.S.C. § 102

Claims 1 and 5 stand rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by Canning et al. (USPN 6,979,442). According to the Examiner, Canning et al. teach stabilized protein pharmaceutical compositions comprising stabilizing buffers, examples of which include EPO and TRIS, respectively.

The Examiner dismissed Applicants' previous rebuttal, citing to *Ex parte A*, 17 USPQ2d 1716 (BPAI, 1990) for the premise that "when a genus is clearly named, the species is anticipated no matter how many others are additionally named." Applicants wish to reiterate that while Canning et al. indeed disclose a genus of pharmaceutical formulations comprised of "a

protein" and "a stabilizing buffer", they never "clearly name" the presently claimed species, a pharmaceutical formulation comprised of erythropoietin (EPO) and tris-(hydroxymethyl)-aminomethane (TRIS). In fact, given that the Canning genus contemplates over 150 possible proteins (see Table 1, col. 10:60-12:25) and over twenty possible stabilizing buffers (see Table 2, col. 13:63-14:35), the claimed combination of EPO and TRIS represents only one out of a possible 30,000 combinations. Accordingly, Applicants reiterate that the likelihood of arriving at a composition comprised of these two select components is indeed analogous to "finding a needle in a haystack" or "discovering the combination of a safe by the inspection of its dials". Moreover, in that neither component of the presently claimed pharmaceutical formulation is separately identified by Canning et al. as preferred or illustrated in any of the recited examples, much less identified as useful together, Applicants respectfully submit that one could arrive at the presently claimed combination only through a meticulous selection of substituents for Canning provides no motivation or guidance. Furthermore, nothing in the Canning reference would lead one to formulate EPO with TRIS in the absence of the amino acid and human serum albumin stabilizers, each of which are described in the prior art as necessary to prevent aggregation in EPO formulations. Accordingly, Applicants respectfully submit that the generic teachings of Canning fail to anticipate or render obvious the invention of the pending claims.

Nevertheless, in an effort to expedite prosecution, Applicants have herewith amended the formulation of claims 1 *et seq*. to specify a pH in the range of 5.9 to 6.8 As noted in the specification at p. 4, lines 1-5, TRIS is used to buffer pharmaceutical formulations in the pH range between 7 and 9. At pH values outside this range, TRIS shows little to no buffering properties.[1] This point is further evidenced by the previously cited Williams reference (US2004/0022861), which describes an insulin particle formulation buffered with TRIS at pH 7.24 (see [0161]).

As noted previously, the burden is on the Examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed

[1] See the www.wikipedia.com entry for "TRIS" ("TRIS has a pKa of 8.3 (at 20 °C), which implies that the buffer has an effective pH range between 7.0 and 9.2.").

invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). Merely suggesting that a reference could be physically modified does not render the resulting modification "obvious" unless the prior art also suggests the desirability of the modification. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). A statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" is not sufficient to establish a *prima facie* case of obviousness without some objective reason to modify or combine the teachings of the reference(s). *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). See also *In re Kotzab,* 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000)

In this case, none of the prior art references provide the requisite motivation or suggestion to (a) formulate EPO with TRIS at a pH between 5.9 and 6.8, or (b) formulate EPO with TRIS in the absence of amino acids and human serum albumin. In fact, following the guidance of the prior art, one would expect either option to result in an unsatisfactory EPO formulation and combining the two options would certainly be expected to result in failure. In that it is well settled that there can be no motivation or suggestion to make a modification that renders the prior art being modified unsuitable or unsatisfactory for its intended purpose, Applicants respectfully submit that the prior art of record, alone or in combination, fail to render obvious the presently claimed invention.

Furthermore, as the instant examples evidence, so formulating EPO gives rise to an unexpected degree of stability and a marked reduction in aggregate formation. Specifically, Applicants compared an illustrative prior art EPO formulation, containing a conventional glycine stabilizer at a standard pH of 7.0, with four inventive EPO formulations, all free of amino acid and BSA stabilizers and three containing varying levels of TRIS (20 to 140 mM) at a pH of 6.5. The results, depicted in Figures 1-4, described at p. 6-7, and summarized below, clearly

demonstrate that formulating EPO with TRIS at a pH outside its optimal range leads to a surprising reduction in aggregate formation.

Formulation	**Degree of Aggregation at 4, 6, and 8 weeks**		
Prior Art (67 mM glycine)	6.11	10.29	---
Invention B (20 mM TRIS)	0.53	1.35	1.98
Invention C (70 mM TRIS)	0.31	0.77	2.14
Invention D (140 mM TRIS)	0.49	1.06	0.13
Degree of Improvement:	≈ 12X to 20X	≈ 8X to 13X	∞

As shown above, formulations containing TRIS at pH 6.5 presented a reduction in aggregation that was eight to twenty times better than that presented by the conventional formulation. Applicants respectfully submit that this unexpected improvement in stability serves as an objective indicia of the non-obviousness of the present invention. Thus, Applicants request reconsideration of the outstanding grounds of rejection.

Rejections under 35 U.S.C. § 103

Konings:

Claim 12 stands rejected under 35 U.S.C. § 103 as being allegedly unpatentable over Canning et al. (USPN 6,979,442) as applied to claim 1, further in view of Konings et al. (USPN 5,376,632). According to the Examiner, while Canning et al. fail to teach a pharmaceutical formulation comprising EPO and TRIS, together with EDTA in an amount ranging from 0.1 to 0.5 mM, the Konings reference cures this deficiency by teaching methods for stabilizing EPO in an aqueous solution, more particularly methods for avoiding the heavy metal catalyzed degradation of

EPO through the inclusion of suitable complexing agents, such as calcium chloride or EDTA, for example at a concentration ranging from 0.2 to 2 g/l (i.e., 0.1 to 0.5 mM). The Examiner thus concludes that it would have been obvious to include the additional components disclosed by Konings in the Canning EPO pharmaceutical formulation to arrive at the invention presently claimed.

The deficiencies of the Canning reference are discussed above. Applicants respectfully that Konings et al. fail to cure the deficiencies of the Canning reference noted in the context of pending claim 1, much less provide the requisite motivation or suggestion for the invention of claim 12. Specifically, the Konings reference fails to provide a motivation to combine EPO with a TRIS stabilizer at a pH of 5.9 to 6.8 in the absence of amino acids and human serum albumin to arrive at the surprising stable pharmaceutical formulation of the pending claims. Accordingly, Applicants respectfully submit that the cited references, alone or in combination, fail to render obvious the invention of the pending claims. Thus, Applicants request reconsideration and withdrawal of the rejection of claim 12 under 35 U.S.C. § 103.

Sharma & Williams:

Claims 1-4, 6-8, and 14 stand rejected under 35 U.S.C. § 103 as being allegedly unpatentable over Canning et al. (USPN 6,979,442) as applied to claim 1, further in view of Sharma et al. (USPA 2003/0148938) and Williams et al. (USPA 2004/0022861). According to the Examiner, while Canning et al. fail to teach a pharmaceutical formulation comprising EPO and 10 - 200 mM TRIS, together with a sodium phosphate buffer and NaCl at a pH ranging from 5.9 to 6.8, more preferably 6.2 to 6.6, the Sharma and Williams references cure these deficiencies. Specifically, Sharma teaches the inclusion in pharmaceutical formulations of sodium phosphate buffers at a concentration of about 10 mM to about 30 mM and at a pH of 4 to 9. Sharma further teaches the use of NaCl at a concentration of about 75 mM to about 100 mM as a tonicity agent. The Examiner cites to Williams for teaching the use of 150 mM TRIS, as well as Tween 80 and NaCl, in the pharmaceutical formulation of proteins such as EPO.

The deficiencies of the Canning reference are discussed above. Applicants respectfully submit that neither Sharma nor Williams cure the deficiencies of the Canning reference noted in the context of pending claim 1, much less provide the requisite motivation or suggestion for the inventions of claims 2-4, 6, 8, or 14. Specifically, neither Williams nor Sharma provide a motivation to combine EPO with a TRIS stabilizer at a pH of 5.9 to 6.8 in the absence of amino acids and human serum albumin to arrive at the surprising stable pharmaceutical formulation of the pending claims. In fact, Williams expressly teaches away from this pH range, citing to the use of TRIS at a pH of 7.24 (see [0161]).

As for the proposed combination of Sharma and Canning, while Sharma may arguably suggest the exchange of Canning's TRIS stabilizing buffer for the sodium phosphate buffer systems disclosed by Sharma, there is certainly no suggestion to modify the Canning composition to formulate a protein composition with both TRIS and sodium phosphate together as pending claim 2 requires. Moreover, Applicants submit that utilizing multiple buffer systems together would be counterintuitive and unduly complex. Buffer solutions resist changes in hydronium ion and the hydroxide ion concentration (and consequently maintain a stable pH) as the result of an equilibrium that arises between a buffers weak acid (HA) and its conjugate base (A-). One typically selects a buffer that has a pKa equal to the pH desired, since a solution of this buffer would contain equal amounts of acid and base and therefore be in the middle of the range of buffering capacity. However, multiple divergent buffering ions in a single system would be expected to interfere and compete and therefore disrupt the delicate equilibrium required for pH stabilization. Accordingly, while one of ordinary skill in the art may have been motivated to use one or the other of TRIS and phosphate to stabilize a pH, there is no reason to expect that the combination of the two would yield a suitably stable, pH buffered pharmaceutical formulation.

Accordingly, Applicants respectfully submit that the cited references, alone or in combination, fail to render obvious the invention of the pending claims. Thus, Applicants request reconsideration and withdrawal of the rejection of claims 1-4, 6, 8, and 14 under 35 U.S.C. § 103.

Cho:

Claims 1, 9-11, and 13 stand rejected under 35 U.S.C. § 103 as being allegedly unpatentable over Canning et al. (USPN 6,979,442) as applied to claim 1, further in view of Cho et al. (USPN 5,656,289). According to the Examiner, while Canning et al. fail to teach a pharmaceutical formulation comprising EPO and TRIS, together with 0.005 to 0.1% w/v polysorbate, the Cho reference cures this deficiency by teaching methods for pharmaceutical formulations comprising EPO and polysorbate 20 or polysorbate 80. The Examiner thus concludes that it would have been obvious to include the additional components disclosed by Cho in the Canning EPO pharmaceutical formulation to arrive at the invention presently claimed.

The deficiencies of the Canning reference are discussed above. Applicants respectfully that Konings et al. fail to cure the deficiencies of the Canning reference noted in the context of pending claim 1, much less provide the requisite motivation or suggestion for the invention of claims 9-11 and 13. Specifically, the Cho reference fails to provide a motivation to combine EPO with a TRIS stabilizer at a pH of 5.9 to 6.8 in the absence of amino acids and human serum albumin to arrive at the surprising stable pharmaceutical formulation of the pending claims. Accordingly, Applicants respectfully submit that the cited references, alone or in combination, fail to render obvious the invention of the pending claims. Thus, Applicants request reconsideration and withdrawal of the rejection of claims 1, 9-11, and 13 under 35 U.S.C. § 103.

In sum, Applicants respectfully submit that the invention of the pending claims is neither anticipated nor rendered obvious by the prior art of record. Accordingly, Applicants submit that pending claims 1-6 and 8-14 are in condition for allowance and respectfully petition for an early indication of such.

CONCLUSION

The outstanding Office Action set a three-month shortened statutory period for response, response being due on or before **April 22, 2008**. Accordingly, Applicant submits that this response is timely and that no additional fee is required. However, in the event that further fees are required to enter the instant response and/or maintain the pendency of this application, the Commissioner is authorized to charge such fees to the undersigned's Deposit Account No. **50-2101**.

If the Examiner has any questions or concerns regarding this communication, she is invited to contact the undersigned.

Respectfully submitted,

Date: April 22, 2008

By: /chalin a. smith/

Smith Patent Consulting, LLC
3309 Duke Street
Alexandria, VA 22314
Telephone: (703) 549-7691
Facsimile: (703) 549-7692

Name: Chalin A. Smith
Title: Attorney for Applicant
Registration No. 41,569

CUSTOMER NUMBER 31,496